



Consumer and
Corporate Affairs Canada

Consommation
et Corporations Canada

(11) (A) No. **1 196 285**
(45) ISSUED 851105

(52) CLASS 167-310

(51) INT. CL. A61K 7/48,9/10,31/07⁴

(19) (CA) **CANADIAN PATENT** (12)

(54) Skin Treatment Compositions

(72) Elliott, Thomas J.;
Murrell, Elspeth A.,
U.K.

(73) Granted to Beecham Group p.l.c.
U.K.

(21) APPLICATION No. 428,133
(22) FILED 830513
(30) PRIORITY DATE U.K. (8214201) 820515

No. OF CLAIMS 31 - NO DRAWING

Canada

ABSTRACT

A skin-care composition comprising a topically acceptable oil-in-water or water-in-oil emulsion base and from 1,000 to 15,000 I Ug⁻¹ of a C₁₋₁₀ alkyl ether or a C₃₋₁₀ alkyl ester of retinol is disclosed. The composition preferably contains an anti-oxidant such as butylated hydroxytoluene or butylated hydroxyanisole. The composition is useful in promoting epidermal mitosis.

SKIN TREATMENT COMPOSITIONS

This invention relates to topical compositions containing esters or ethers of retinol which are useful in the care of skin.

British Patent Specification No. 1,489,133 describes and claims a liquid, semi-liquid or gel composition comprising a topically acceptable oil-in-water or water-in-oil emulsion base and retinol acetate in an amount from 1,000 to 15,000 IUg⁻¹. Such compositions are of value in promoting epidermal mitosis and thus lead to a desirable thickening or
10 aplumping effect on the skin.

Published British Patent Application No. 2,026,319 describes and claims a similar composition to that of Specification No. 1,489,133, wherein the formulation of the emulsion base leads to high activity in skin thickening.



Although the compositions disclosed in the above two patent specifications give an enhanced skin thickening effect, the retinol acetate tends to decompose over a period of time, hence reducing the shelf life of the product. The decomposition is due largely to hydrolysis of the acetate by water in the emulsion base, followed by rapid oxidation of the free retinol. Furthermore, since retinol acetate is water insoluble it is normally mixed with a non-ionic surfactant, thereby forming a water soluble form, prior to incorporation into the emulsion base.

It has now been found that acceptable levels of skin thickening coupled with good stability can be obtained if a C₁₋₁₀-alkyl ether or a C₃₋₁₀-alkyl ester of retinol is used in place of retinol acetate. It has also been found that the C₁₋₁₀ ether or C₃₋₁₀ ester of retinol may be incorporated into an emulsion base either as a water soluble or water insoluble form.

Accordingly, the present invention provides a skin-care composition, comprising a topically acceptable oil-in-water or water-in-oil emulsion base and from 1,000 to 15,000 I Ug⁻¹ of a C₃₋₁₀ alkyl ester or a C₁₋₁₀ alkyl ether of retinol.

Preferably, the composition of the invention comprises the all trans- isomer of a C₁₋₁₀ alkyl ether or a C₃₋₁₀ alkyl ester of retinol.

Preferably, the composition comprises a C₃₋₇ straight chain, branched chain, or cyclo- alkyl ester of retinol; for example retinol propionate, butyrate, cyclopentanecarboxylate, pivalate, valerate, hexanoate, and heptanoate.

Preferred ethers of retinol for use in the composition of the invention are C₁₋₇ alkyl ethers, suitably the methyl ether of retinol is used.

Preferably, the composition comprises from 1,000 to 10,000 I Ug⁻¹, or more suitably from 2,000 to 5,000 I Ug⁻¹ of a C₁₋₁₀ alkyl ether or a C₃₋₁₀ alkyl ester of retinol.

10 The preferred emulsion base is an oil-in-water emulsion base containing from 20 to 40% by weight of oil.

An emulsifier is preferably used in the composition of the invention, and this may be an anionic, cationic or non-ionic type. In order of their ability to produce a skin thickening effect, anionic emulsifiers are less effective than non-ionic emulsifiers which are in turn less effective than cationic emulsifiers. However, the latter can cause skin irritation when used, and non-ionic emulsifiers are, therefore, preferred.

20 It has been found that the proportion of non-ionic emulsifier in the compositions of the invention is not critical, but at least 1% by weight is preferred to give a stable emulsion. Suitably an amount in the range 2% to 12%, more suitably 4% to 8% is preferred.

30 Examples of oils suitable for inclusion in the present compositions include: volatile linear iso-paraffins, acyclic dimethylpoly siloxanes, cyclic dimethylpoly siloxanes, mineral oils, vegetable oils, synthetic fatty acid esters, fatty alcohols, lanolin and its derivatives.

Examples of non-ionic emulsifiers suitable for inclusion in the present compositions include:

sorbitan monostearate, glyceryl monostearate, polysorbates, polyethylene derivatives of fatty alcohols.

The compositions of this invention should desirably include an anti-oxidant effective in preventing oxidation of the retinol component and consequent reduction in the activity of the composition. Some anti-oxidants are effective in this respect but themselves oxidise to give a noticeable yellowing of the cream.

Two anti-oxidants which are particularly suitable for incorporation are butylated hydroxytoluene (BHT), (2,6-di-tert-butyl-p-cresol) and butylated hydroxyanisole (BHA), (2-tert-butyl-4-hydroxyanisole or 3-tert-butyl-4-hydroxyanisole) or a mixture of these. Accordingly in another of its aspects, the invention includes a composition in accordance with the invention including BHT and/or BHA as anti-oxidant.

The retinol component of the compositions may be dispersed in the emulsion in the form of a 'solubilised' mixture. Such mixtures are generally solutions of the retinol component in hydrophilic organic solvents such as glycerine and/or propylene glycol, together with a surfactant such as Tween 80.

The invention also provides a process for preparing a skin-care composition comprising a topically acceptable oil-in-water or water-in-oil emulsion base and from 1,000 to 15,000 I Ug⁻¹ of a

C₃-10 alkyl ester or a C₁-10 alkyl ether of retinol, which comprises mixing the emulsion base with the retinol component.

Preferably, the retinol component is added to the emulsion base with stirring at a temperature of less than 50°C, suitably 35°C.

The C₁-10 alkyl ethers and C₃-10 alkyl esters of retinol are known compounds or can be prepared by procedures analogous to known preparative procedures.

- 10 The present invention further provides a method of treatment of the skin of the human or animal body, comprising the topical application of a skin-care composition of the present invention.

The following are examples of compositions in accordance with the invention.

Example 1

Formulation

	<u>% w/w</u>
Sorbitan stearate	2.00
Polysorbate 60	2.00
20 Cetyl alcohol	2.00
Cetyl alcohol/PEG 40 Castor Oil	2.50
Mineral Oil	25.00
Lanolin	2.50
Decyl oleate	2.00
Preservatives	0.37
Anti-oxidant (BHT)	0.20
Perfume	0.45
Water soluble retinol propionate	3,000 - 7,000 IU/g
Deionised water to	100,00

Sorbiton stearate, polysorbate 60, cetyl alcohol, PEG 40 castor oil, mineral oil, lanolin, decyl oleate, anti-oxidant, and preservatives were blended together and heated to about 78°C. The mixture was added to water at 78°C with stirring. The mixture was homogenised then allowed to cool to 35°C.

Retinol propionate was added to the mixture with stirring. The mixture was again homogenised, then cooled to 25°C. Perfume was added with stirring.

- 10 The following Examples were prepared using a procedure analogous to that used in Example 1.

Example 2

		<u>% w/w</u>
	Glyceryl stearate/PEG 100 Stearate	4.50
	Cetostearyl alcohol	4.50
	Cetearyl octanoate	3.00
	Stearyl heptanoate	2.00
	Fatty acid ester of propylene glycol	4.00
	Mineral oil/lanolin alcohol	3.00
	Octyl palmitate	5.00
20	Mineral oil	5.00
	Antioxidant (BHT)	0.20
	Propylene glycol	3.00
	Preservatives	0.62
	Perfume	0.20
	Water soluble retinol	3,000 - 7,000 IU/g
	cyclopentanoate	
	Deionised water to	100.00

Example 3

		<u>% w/w</u>
	Ceteareth 12	2.00
	Cetyl alcohol	8.00
	Squalane	10.00
	Antioxidant (BHT)	0.20
	Propylene glycol	2.00
	Preservatives	0.37
	Perfume	0.30
	Oil soluble retinol methyl ether	3,000 -7,000 IU/g
10	Deionised water to	100.00

Example 4

		<u>% w/w</u>
	Sorbitan stearate	1.50
	Polysorbate 60	2.00
	Glyceryl stearate	4.00
	Cetyl alcohol	2.00
	Octyl palmitate	3.00
	Mineral oil	8.00
	Decyl oleate	3.00
	Anti-oxidant (BHT)	0.10
20	Polyethylene microspheres	3.00
	Glycerine	5.00
	Allantoin	0.10
	Propylene glycol	3.00
	Preservatives	0.35
	Oil soluble retinol heptanoate	3,000 - 7,000 IU/g
	Perfume	0.20
	Deionised water to	100.00

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE
PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for preparing a skin-care composition comprising a topically acceptable oil-in-water or water-in-oil emulsion base and from 1,000 to 15,000 I Ug⁻¹ of a C₃₋₁₀ alkyl ester or a C₁₋₁₀ alkyl ether of retinol, which process comprises mixing the emulsion base with the retinol component.
2. A process as claimed in claim 1, wherein the retinol component is in the all trans-form.
3. A process as claimed in claim 2, wherein the retinol component is a straight chain, branched chain, or cyclic C₃₋₇ alkyl ester of retinol.
4. A process as claimed in claim 2, wherein the retinol component is a C₁₋₇ alkyl ether of retinol.
5. A process as claimed in claim 1, 3 or 4, wherein the amount of the retinol component is from 1,000 to 10,000 I Ug⁻¹.
6. A process as claimed in claim 1, 3 or 4, wherein the amount of the retinol component is from 2,000 to 5,000 I Ug⁻¹.
7. A process as claimed in claim 1, 3 or 4, wherein the emulsion base comprises from 20 to 40% by weight of oil.
8. A process as claimed in claim 1, 3 or 4, comprising the addition of an emulsifying agent.
9. A process as claimed in claim 1, 3 or 4, comprising the addition of an emulsifying agent which is a non-ionic emulsifying agent.
10. A process as claimed in claim 1, 3 or 4, comprising the addition of an anti-oxidant.

5404-1



11. A process as claimed in claim 1, wherein the retinol component is an ester selected from retinol proprionate, butyrate, cyclopentanecarboxylate, pivalate, valerate, hexanoate and heptanoate.
12. A process as claimed in claim 1, wherein the retinol component is the methyl ether of retinol.
13. A composition for skin-care comprising a topically acceptable oil-in-water or water-in-oil emulsion base and from 1,000 to 15,000 I Ug⁻¹ of a C₃₋₁₀ alkyl ester or a C₁₋₁₀ alkyl ether of retinol.
14. A composition as claimed in claim 13, wherein the retinol component is in the all trans-form.
15. A composition as claimed in claim 14, wherein the retinol component is a straight chain, branched chain, or cyclic C₃₋₇ alkyl ester of retinol.
16. A composition as claimed in claim 15, wherein the retinol component is an ester selected from retinol proprionate, butyrate, cyclopentanecarboxylate, pivalate, valerate, hexanoate and heptanoate.
17. A composition as claimed in claim 14, wherein the retinol component is a C₁₋₇ alkyl ether of retinol.
18. A composition as claimed in claim 17 wherein the retinol component is the methyl ether of retinol.
19. A composition as claimed in claim 13, 16 or 18, wherein the amount of the retinol component is from 1,000 to 10,000 I Ug⁻¹.
20. A composition as claimed in claim 13, 16 or 18, wherein the amount of the retinol component is from 2,000 to 5,000 I Ug⁻¹.
21. A composition as claimed in claim 13, 16 or 18, wherein the emulsion base comprises from 20 to 40% by weight of oil.

22. A composition as claimed in claim 13, 16 or 18, wherein the amount of the retinol component is from 1,000 to 10,000 I Ug⁻¹ and the emulsion base comprises from 20 to 40% by weight of oil.

23. A composition as claimed in claim 13, 16 or 18, wherein the amount of the retinol component is from 2,000 to 5,000 I Ug⁻¹ and the emulsion base comprises from 20 to 40% by weight of oil.

24. A composition as claimed in claim 13, 16 or 18, wherein there is also present an emulsifying agent.

25. A composition as claimed in claim 13, 16 or 18, wherein there is also present a non-ionic emulsifying agent.


26. A composition as claimed in claim 13, 16 or 18, wherein there is also present a non-ionic emulsifying agent, the emulsion base comprises from 20 to 40% by weight of oil and the amount of the retinol component is from 1,000 to 10,000 I Ug⁻¹.

27. A composition as claimed in claim 13, 16 or 18, wherein there is also present a non-ionic emulsifying agent, the emulsion base comprises from 20 to 40% by weight of oil and the amount of the retinol component is from 2,000 to 5,000 I Ug⁻¹.

28. A composition as claimed in claim 13, 16 or 18, wherein there is also present an antioxidant.

29. A composition as claimed in claim 13, 16 or 18, wherein there are also present an emulsifying agent and an antioxidant.

30. A composition as claimed in claim 13, 16 or 18, wherein there are also present an emulsifying agent and an antioxidant, the emulsion base comprises from 20 to 40% by weight of oil and the amount of the retinol component is from 1,000 to 10,000 I Ug⁻¹.



1196285

-11-

31. A composition as claimed in claim 13, 16 or 18, wherein there are also present an emulsifying agent and an antioxidant, the emulsion base comprises from 20 to 40% by weight of oil and the amount of the retinol component is from 2,000 to 5,000 I Ug⁻¹.



5405-1

A

